ARGUMENT

Rejection of Claims 403-405 and 407-412 under 35 U.S.C. §112, Second Paragraph – Indefiniteness

Claims 403-405 and 407-412 stand rejected as indefinite under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the invention. Specifically, the PTO contends that step (b) in calling for "forming a bud" is indefinite since it not clear what action is required by the practitioner in performing the recited method. The Examiner contends that the specification fails to "provide any teaching specifically directed to forming a bud." Applicant disagrees that the subject matter of claims 403-405 and 407-412 lacks the definiteness required by Section 112 of the Statute.

The Office Action incorrectly contends that the specification only teaches forming a tooth bud. The Examiner is correct in stating that the specification does not teach that a "special act" is required to form a bud or to grow an artery from said bud. The specification at page 31, lines 18-26 discloses that once the composition required for forming the desired tissue is implanted in the patient at a desired location a bud is formed which grows via morphogenesis into the desired tissue. The specification at page 39, Example 3, also teaches selecting cells for implantation that contain the active growth and transcription factors required for forming the desired "bud" in vivo which grows morphogenetically into the desired tissue. The patient's body completes the formation of the desired tissue along predetermined genetic pathways. A tooth is a multiple tissue organ which includes blood vessels, nerves, etc, and to the learned individual provides a microcosm into human physiology. A skilled person having experience in the medical arts reading the instant specification would understand that the formation of a bud/ primordium is the foundation for human organogenesis. In this regard, see Paragraph 5 of the Declarations of Drs.

C. Gene Wheeler, Wayne H. Finley, and Andrew E. Lorincz (all of record). It is clear that one having experience in the medical arts reading the specification would understand that it teaches an embodiment comprising forming a primordium as a precorsor in growing both soft and hard tissue (see Paragraph 7 of the above-mentioned Declarations of Drs. C. Gene Wheeler, Wayne H. Finley, and Andrew E. Lorincz.) This is consistent with the disclosure at page 31 wherein the specification describes the term "bud" as designating a partially grown tooth and Examples 15 and 17 which describe the role of cells in developing organs. Moreover, it is clear from said Declarations and the specification as a whole that Dr. Elia recognized that stem cells are biological building blocks that promote the growth of cells/tissues in the body.

Finally, the question/issue of whether instant claims 403-405 and 407-412 are definite within the purview of the second paragraph of Section 112 does not depend on their relationship with the scope of claims in co-pending application Serial No. 10/179, 389. The subject matter of the instant claims is defined by language requiring that the implanted composition forms a bud via morphogenesis along predetermined genetic pathways, which bud grows into the desired soft tissue thus providing the desired functional outcome. The lack of clarity posited by the Examiner in ¶7, page 5 is a product of the Examiner's refusal to read and understand the specification as well as the record as a whole. Applicant's specification recognizes that there are multiple pathways via which cell regeneration occurs—direct cell differentiation from mononuclear cells and stimulation of endogenous cells at the site of implantation are clearly described. This is consistent with the observations of the 2005 publication of Strauer et al. in Circulation at pages 1656 and 1657 entitled, "Regeneration of Human Infarcted Heart Muscle by Intracoronary Autologous Bone Marrow Cell Transplantation in Chronic Coronary Artery Disease" (hereinafter "Strauer 2005" and of record) that cell regeneration may be explained by as

many as four mechanisms. There is no requirement that Applicant limit the claims to any particular growth mechanism. All that is required by the second paragraph is that the claims define the intended invention with a reasonable degree of clarity. Applicant submits that a reasoned reading of the claim language in light of the instant specification compels a conclusion that the claims satisfy the definiteness requirement of the Statute.

Accordingly, Applicant does not believe that it is necessary to amend the claims as suggested by the PTO at page 3 of the Office Action to overcome this rejection. However, should the Board of Appeals and Patent Interferences following a decision for any subsequent appeal believe that such amendment is required to overcome the rejection, Applicant stands ready to make the suggested amendment.

Rejection of Claim 404 under 35 U.S.C. §112, First Paragraph – Description

Claim 404 stands rejected under 35 U.S.C. §112, first paragraph for failure to satisfy the "written description" requirement. Specifically, the PTO maintains that the specification fails to provide an adequate description of the limitations commensurate with the specific scope of protection sought by the claim in issue – that the specification fails to *in haec verba* describe "…growing an artery by administration of stem cells to a damaged site in a leg of a patient…"

The Office Action, in particular, points out that no claim reciting "stem cell" and "artery" is rejected for lack of description. The PTO apparently concedes that the specification generally describes the general inventive concept of injecting stem cells for growth of an artery, and for good reason. The PTO rejection admits that pages 47-48 of the specification describes stem cells as an example of a patient's own cells that are contemplated for producing an artery via direct differentiation and morphogenesis as a desired functional outcome. It is also noted that the PTO

has not challenged Applicant's position that Example 18 of the specification describes a method of growing an artery in the leg of a patient by injecting a composition which is described in the specification as belonging to a class of compositions that promote soft tissue growth. It is clear that this example describes every limitation called for by claim 404 except the use of stem cells as the injectable composition for promoting the desired soft tissue growth.

The standard for written description applied by the PTO in rejecting claim 404 is tantamount to requiring the specification establish literal support for the claimed combination of features. It is trite law that a specification need not set forth a distinct embodiment corresponding to every claim at issue. Cf. Union Oil of Cal. v. Atlantic Richfield Co., 208 F3d 989, 997, 54 USPQ 1227, 1232-33 (Fed. Cir. 2000). It is enough for the purposes of the written description requirement of Section 112 of the Statute that the specification contain an equivalent description of the claimed subject matter sufficient to convey to one having experience in the medical arts that applicant was in possession of the claimed invention, i.e., locally injecting a class of artery growth promoting compositions encompassing a patient's own stem cells at a desired site in the patient's leg. See in particular Lockwood v. American Airlines, Inc., 107 F3d.1505, at 1572, 41 USPQ 2d. 1961 (Fed. Cir. 1997).

The present PTO Examiner in ¶10 attempts to explain the rationale for this rejection-that there is no literal teaching in the specification of the concept of injecting a cell at a damaged site in a patient's leg to facilitate artery growth. As set forth above this is not the legal/statutory standard. The instant specification is replete with disclosure relating to injecting soft tissue promoters at a site in the leg of a patient to facilitate the growth of an artery. Pages 47 and 48 describe implanting a patient's own cells, such as autologous stem cells, in situations where growth of an artery is a desired functional outcome. The present PTO Examiner has failed to

adequately explain why a person of skill reading the specification as a whole would not have reasonably understood that Applicant was in possession of the concept of using either genes or cells as injectable soft tissue promoters for facilitating artery growth.

The present PTO Examiner's attempt to discredit Applicants teaching of using cells to promote artery growth by belatedly attacking Applicant's use of the term "growth factor" is inept. The specification clearly defines the term "growth factor" as comprising compositions that promote growth of soft and hard tissues. All claims under prosecution recite implanting cells to facilitate soft tissue growth. The present PTO Examiner's criticism (¶13) that the concept that cells fall within the definition on page 20 of the specification first appears in the Heuser and Lorincz Supplemental Declarations is disingenuous, at best. It is clear from Paragraphs 3-7 of the Heuser declaration, for example, that declarant after reading the specification understood that Applicant contemplated implanting a growth factor comprising cells, such as, stem cells to grow an artery. This is clearly a recognition "that Declarant recognized a concept that cells are a species of growth factor in the specification as filed." Dr. Heuser's recognition that the term "growth factor"used in Applicant's specification included cells and stem cells clearly meets the test for descriptive compliance set forth in the Multiform Dessicants, Inc. case cited by the PTO. Dr. Heuser is a person of experience in the field of regenerative medicine. As for the Alberts definition of growth factor, which concurs with Applicant's specification, there is nothing in this publication that prevents cells from being growth factors. Strauer 2005 teaches that mononuclear cells stimulate endogeneous cells to differentiate and regenerate. This criticism is evidence that the PTO has incorrectly viewed the prosecution of Applicant's cases as an exercise of acumen or shrewdness, not a process which follows standardized administrative procedures sanctioned by the APA. Patent prosecution at the administrative level is a "fee for service" endeavor designed

to be conducted under non adversarial conditions with fairness and due process guarantees owed to applicants.

Applicant notes that the present PTO Examiner has abandoned his Ruschig analysis in light of Applicant's remarks and for good reason. The declaration evidence affirms that the claim at issue is drawn from Applicants specification itself which describes a class of compositions for promoting the growth of soft tissue, which broadly includes cells and more specifically bone marrow stem cells. The specification at page 37 teaches that cellular products are growth factors. The specification also discloses using a patient's own bone marrow as a source of autologous stem cells for promoting growth of an artery via differentiation and morphogenesis. Page 44, lines 22-24 of the specification contemplates using VEGF "or its growth factor equivalent" for promoting artery growth. It is clear that all the claimed limitations appear as words in the specification. Accordingly, the necessary blaze marks directing one having experience in the medical arts desiring to practice the protocol of Example 18 to inject a cellular growth factor, such as a patient's own stem cells, as an alternative composition for promoting artery growth in a patient's leg exhibiting vascular damage is clearly provided by the instant specification.

The PTO argues that while the disclosure on pages 47 and 48 of the specification teaches using stem cells (e.g., autologous stem cells) for growing an artery among other organs, it does not describe treating a damaged site in a leg. A person of experience in the medical arts reading the specification would understand that growing an artery in the leg of a patient is one of the desired functional outcomes of the invention described in the specification. Aside from the written description set forth in the specification, skilled medical practitioners, Drs. Richard Heuser and Andrew E. Lorincz, declared that the specification taught them that the described

administrative techniques, including injection, would be useful for implanting the growth factor compositions disclosed in the specification, such as stem cells, for growing an artery in a patient. See Paragraph 5 of the Declaration of Dr. Heuser and Paragraph 6 of the Supplemental Declaration of Dr. Lorincz (both of record).

At ¶13, pages 9 and 10 of the Office Action, the PTO questions whether one experienced in the medical arts reading the specification would understand that Applicant's usage of the term growth factor was intended to include compositions comprising genes and bone marrow stem cells. Lest there be any doubt whether the answer is positive, one need look no further than Paragraphs 5-7 of the Declarations of Drs. Wheeler, Finley, and Lorincz, Paragraph 6 of the Declaration of Dr. Heuser, the Supplemental Declaration of Dr. Lorincz, and the definition found in the Alberts et al. publication definition of "growth factor" cited and made of record by the present PTO Examiner in co-pending Application Serial No. 09/836,750 and entitled, Molecular Biology of the Cell, 4th Ed., Chapter 17 (hereinafter "Alberts" and of record). Alberts' definition of a growth factor is consistent with Applicant's definition found on page 43, lines 18 and 19 of the specification, "Growth factors control cell growth, division, differentiation, migration, structure, function, and self-assembly." Moreover, the PTO, in making restriction requirements prior to and subsequent to the date of the instant Office Action, has consistently identified genes and cells as species of the genus "growth factor". The present PTO Examiner apparently has decided to not accord full faith and credit to such PTO determinations. Accordingly, Applicant is mystified by the present PTO Examiner's insistence upon burdening the record with petty issues that were thoroughly vetted previously by the PTO, via Petition to the Commissioner in the instant application, and subsequently followed by the PTO.

The PTO, by applying strict rules derived from a misapplication of legal precedents, is attempting to use the written description requirement to eviscerate a claim narrowed during prosecution based on a broader disclosed invention. The court in Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 227 USPQ 177 (Fed. Cir. 1985) noted that a combination of features in a claim need not exactly respond to those in the specification- the issue is whether one of skill in the art could derive the claimed combination from the specification. All that is required is that the specification provide enough disclosure to show that Applicant "invented what is claimed." See Vas-Cath, Inc. v. Mahur-kar, 935 F.2d 1555, 1563-64, 19 USPQ2d 111, 1117 (Fed. Cir. 1991). Written description determinations are fact-sensitive and should be dealt with on a case-by-case basis without adhering to strict rules. Also see In re Wertheim, 541 F.2d 265, 191 USPQ 90, 96 (CCPA 1976) wherein the court held that the claimed combination did not have to find verbatim support in the specification. Applicant believes that the Ralston Purina and Wertheim decisions govern this case. Applicant submits that the rejection should be reversed because the record shows substantial evidence of adequate written disclosure for claim 404.

Rejection of Claims 403-405 and 407-412
under 35 U.S.C. §112, First Paragraph – Enablement

Claims 403-405 and 407-412 stand finally rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Applicant responds to the rejection of claims 403-405 and 407-412 in the following three sections, wherein patentability is argued separately in each section.

Being that the relied-upon portions of the prior office actions, if any, have not been specifically identified because the PTO simply stated that the enablement rejection was maintained "for reasons of record", Applicant believes that there is no other option than to repeat

appropriate sections of the Appeal Brief. For the convenience of the PTO, repeated sections will be referenced by referral to the February 26, 2009 Office Action (hereinafter "the 02/26/09 Office Action").

Rejection of Claims 403, 411, and 412
under 35 U.S.C. §112, First Paragraph – Enablement

Claims 403, 411, and 412 stand finally rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Applicant disagrees that the subject specification fails to enable the claimed subject matter under current law. Applicant herein argues the patentability of each claim.

It is well settled that enablement issues are determined by consideration of an applicant's specification along with knowledge in the art at the time of filing, United States v. Telectronics, 857 F. 2d 778, 785; 8 USPQ 2d 1217, 1223 (Fed. Cir.1988, *cert. denied* 490 U.S. 1946 (1989). Applicant submits that the instant specification, when considered in view of the knowledge in the art at the time the application was filed, enables one skilled in the medical art to make and use the claimed invention.

Applicant submits that there are three major points to consider when determining whether the instant specification contains a disclosure that would have enabled a skilled person in the medical art to make and use the claimed invention within the purview of the statute. The points are: 1) the specification disclosure; 2) the knowledge in the art at the time the application was filed; and 3) the skill level in the art. When these points are considered, there should be no doubt that Applicant's specification provides an enabling disclosure.

As to the first point, there is a considerable body of disclosure provided by the subject application relating to Applicant's disclosed invention of promoting the growth of soft or hard

tissue in human patients—including growing a new artery as called for by the claims at issue—by administering a broad class of growth factors, including stem cells, suitable for effecting such tissue growth. Note that Applicant's specification (pages 10, 20, 21, 30-33, and 37-52) provides a substantial body of disclosure regarding using a growth factor to form a bud and thus grow soft tissue in a human body. These portions of the specification describe a class of claimed and unclaimed growth factors that broadly and specifically include genes, nucleic acids, a patient's own cells (autologous cells), or universal cells, e.g., stem cells (global mononuclear bone marrow cells), etc., all of which are described to promote tissue growth through differentiation and morphogenesis. Applicant's broad and specific disclosure relating to the aforementioned class of growth factors patently provides a scope of enablement which includes stem cells broadly (pages 37, 48, 50, and 51) and bone marrow mononuclear stem cells specifically (pages 40-42). Such disclosure is commensurate in scope with the subject matter of the claims at issue.

As to the second point, the record clearly establishes that the administration techniques, apparatus, and administered compositions disclosed and claimed by Applicant were old and well known as of the filing date of the instant patent application.

U. S. Patent No. 5,980,887 to Isner et al. (hereinafter "Isner" and of record) and the Asahara et al. publication, cited in Isner, published in Science and entitled "Isolation of Putative Progenitor Endothelial Cells for Angiogenesis" (hereinafter "Asahara" and of record) constitute contemporary prior art knowledge which employed a limited subpopulation of EC progenitor stem cells isolated from human peripheral blood for promoting capillary growth. Isner and Asahara are evidence that those skilled in the art prior to the Applicant's 1998 filing date were aware that EC progenitor cells (stem cells) and DNA encoding VEGF are alternatives for treating blood vessel injuries, i.e., ischemic tissue. Isner, at column 7, lines 17-23 of the patent, discloses

that "any suitable means" can be used to administer stem cells, including intramuscular injection. U.S. Patent No. 5,328,470 to Nabel et al. (hereinafter "Nabel" and of record) teaches one skilled in the art that cells and genes can be either locally (injection) or systemically administered to human patients to treat organs affected by disease, including ischemic tissue. Although these patents are directed to different inventions than that of Applicant, i.e., employ different cells and achieve different results, they nevertheless apprise one skilled in the art of prior art methods commonly used for administering genes and cells for the treatment of human diseases involving ischemic tissue. Such objective evidence must be taken into consideration by the PTO when determining enablement under 35 U.S.C. §112, first paragraph.

One skilled in the art reading the instant specification's teaching of using stem cells harvested from the bone marrow or blood of the patient would understand that the claimed invention distinguishes from Isner by describing using unfractionated (global) bone marrow mononuclear cells and in achieving a different functional outcome. There is no basis in fact for determining that a fractionated population, such as EC progenitor cells, is disclosed by Applicant because there is no disclosure that the harvested cells are separated and then a separated portion administered to a patient. Reading the disclosure otherwise distorts the reasonable/intended reading of Applicant's specification. Isner serves to apprise one skilled in the art of general methods for implanting endothelial progenitor stem cells for forming capillary blood vessels and restore the endothelial lining of blood vessels. One skilled in the art being so apprised and reading the instant specification would understand that Applicant has provided sufficient information, i.e., the process steps and ingredients essential to grow an artery as set forth in the claims.

Further evidence supporting enablement may be found in the form of the February 13, 2001 Declaration of Dr. G. Robert Meger (of record) which demonstrates that the disclosed and claimed administration techniques used in practicing the invention were known at the filing date of the application. The administration techniques disclosed by Applicant were routinely employed in the medical art, but not in the claimed combination with the claimed materials, at the time the instant application was filed. See in particular the discussion in Isner and Asahara in regard to the medical art's prior use of bone marrow transplants (HSCs) in treating diseases. Isner acknowledges using techniques similar to those used in the medical arts for recovering HSCs in obtaining endothelial progenitor cells (CD34+). The collection, handling, and reimplantation of HSCs are so well known and notorious in the medical arts that the PTO should take Official Notice of same.

In any event, Applicant submits that such disclosure of the instant specification and existing knowledge in the art, such as that identified by Dr. Meger, as well as the work of Isner, Asahara, and Nabel, would enable a skilled practitioner to practice the claimed invention. As will become evident later, two experts in the medical field, Drs. Richard Heuser and Andrew E. Lorincz, being apprised of relevant portions of Applicant's specification, confirm such conclusion.

As to the third point, the PTO has acknowledged that the level of skill in the medical art is high. Applicant agrees that the skill level is high when it is considered that many years of education, training, and experience are required in the medical field. The instant specification is thus addressed to, and consequently would be understood by, such highly skilled persons.

Once the above-identified relevant materials and administration techniques set forth in the subject specification are properly considered in their entirety, Applicant believes that there

should be no question that one skilled in the medical art is enabled to make and use the claimed invention. This conclusion is reinforced, as noted above, by the fact that the materials and administration techniques, but not the inventive results, were well known when the instant application was filed. MPEP Section 2164 states that the purpose of the enablement requirement is to describe the claimed invention in such terms to permit one skilled in the art to make and use the invention. Such Section cautions that detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention. For the reader's convenience, MPEP Section 2164.01 states that:

> A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F2d. 660, 661, 18 USPQ 2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d. 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) cert denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 730 F2d. 1452, 1463, 221 USPQ 481, 489 (Fed. Cir.1984).

Applicant believes that the above caution is especially relevant to the instant factual situation where the Examiner has conceded that there was a high level of skill in the art at the time the instant application was filed and further in view of the evidence contained in Isner, Asahara, Nabel, and Dr. Meger's Declaration that the methods and apparatus needed to practice the invention were well known at the time of the invention. Thus, Applicant submits that the instant disclosure clearly enables one skilled in the medical art to make and/or use the full scope of the claimed invention without undue experimentation. Any reasonable consideration of the three above-delineated points and the interaction thereof compels such conclusion.

Applicant's above conclusion that one skilled in the art is enabled to make and use the claimed invention is consistent with the PTO's acknowledgement at page 14, ¶18 of the Final

Rejection of May 5, 2008 that the state of the art after the Isner disclosure was such that Applicant's claimed "...method was known to be possible." (of record). Accordingly, the enablement issue should be put to rest because the Isner and Asahara disclosures are prior to, or contemporary with, the filing date of the instant application.

The PTO has the burden to establish and support by convincing objective evidence a *prima facie* case of lack of enablement. For reasons set forth below, Applicant believes the PTO has failed to meet such burden.

The first paragraph of the statue requires nothing more than objective enablement, and it is of no importance whether such teaching is set forth by use of illustrative examples or by broad terminology. As a general matter, an application's disclosure, which contains a teaching of how to make and use the invention in terms which correspond in scope to those used in describing the invention sought to be patented, is considered to be in compliance with the enabling requirement of the statue. In re Marzocchi, 439 F.2d 220, 169 USPQ 367, 369-370 (CCPA, 1971). Further, "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." [Emphasis added]. In re Robins, 429 F.2d 452, 166 USPQ 552 (CCPA, 1970).

Turning to the reasons proffered by the PTO regarding non-enablement, Applicant presents the following remarks.

The PTO, at pages 10 and 11 of the 02/26/09 Office Action, stated that, "The rejection of record has found that *the breadth of the claims* and *the amount of direction and guidance present and the presence or absence of working examples* are the principle [sic] factors that speak against the enablement for the claims under consideration." These factors are discussed below in rebuttal to the lack of enablement rejection.

When evaluating enablement, it is incumbent upon the PTO to determine what subject matter each claim recites, i.e., the scope of protection sought for each claim. The scope of dependent claims are properly determined with respect to 35 U.S.C. §112, fourth paragraph. See MPEP Section 2164.08. It is submitted that the PTO has failed to perform such required analysis. Applicant notes that the PTO has not addressed the subject matter of each claim separately, but instead at page 11, ¶13 of the 02/26/09 Office Action asserted that the elements that are essential and common to all of the claims are not enabled by the disclosure. However, beyond such general assertion, the PTO has not explained why stem cells harvested from bone marrow (claim 407) or stem cells harvested from blood (claim 409) of from the patient (claims 408 and 410) are common to the generic term "stem cells" in the sense of enablement. Applicant has argued that the subject matter of all claims finds enabling support in the specification.

Applicant further points out that it is evident the PTO failed to consider the disclosure provided by the subject specification as a whole in determining compliance with the enablement requirement of the statute. The appropriate factual determination is whether the instant specification reasonably directs one skilled in the art how to make and use the claimed subject matter. The PTO erroneously restricted the factual determination to the elected species of growth factor and, thusly, ignored those portions of the specification describing a broader generic invention and also ignored disclosure related to non-elected species. Applicant is entitled to have the entire disclosure considered in determining compliance with 35 U.S.C. §112, first paragraph. See In re Anderson, supra and In re Johnson and Farnham, supra and such determination must take into consideration that which is known in the prior art--that a patent should preferably omit that which is well known/understood in the particular art to which the claims are directed.

The PTO at pages 11-15, ¶¶14-16 of the 02/26/09 Office Action, asserts that the specification does not disclose with specificity which cells would or would not work for growing an artery. The PTO's above assertion that an applicant must disclose with specificity which cells would not form an artery is erroneous. An applicant is required to provide information that would enable one skilled in the art to which the invention pertains to make and use the claimed invention and is not required to provide information that would not enable one skilled in the art to make and use such invention; i.e., to form an artery.

In any event, the PTO has alleged that the term "stem cells" encompasses a large subgenus of cells and thus somehow does not advise the skilled person which stem cells to use or not to use. When one reads Applicant's specification with the eyes and understanding of a person skilled in the medical art, there should be no question that such person is informed as to the types of stem cells that grow multiple tissue organs, such as an artery. To grow an artery one must use pluripotent stem cells because growth of an artery comprises multiple tissues including muscle and endothelial tissue. Those skilled in the art recognize such elementary fact. The specification teaches on pages 40-42, 47, and 48 utilizing autologous stem cells harvested from bone marrow and blood of the patient (self-cell therapy) or from cell cultures (allogenic) to grow organs, i.e., arteries, by differentiation and morphogenesis (page 48). There can be no doubt that the specification teaches that bone marrow cells promote the growth of organs. Further, the specification on page 50 specifically discloses that implanted pluripotent growth factors direct adjacent cells to reconstruct body parts along genetically predetermined pathways. Those skilled in the art would recognize that bone marrow would comprise pluripotent stem cells. In addition, the skilled person is informed by the specification that pluripotent cells, such as some stem cells, are required for growing organs requiring multiple tissues. Moreover, those skilled in the

medical art are well aware that bone marrow comprises pluripotent stem cells. In this regard, see the internet article cited by the present PTO Examiner in the 02/26/09 Office Action published in The Journal of Invasive Cardiology, Vol. 17, July 1, 2005, entitled "Progenitor Cell Transplantation and Function following Myocardial Infarction." (of record). Applicant attaches the complete article because the present PTO Examiner did furnish a complete copy, and the referred-to passage was omitted from the copy furnished by the present PTO Examiner. Accordingly, one skilled in the art reading the subject specification, would understand that all that is required to practice the claimed invention is to use pluripotent stem cells, such as those disclosed in the instant specification, to grow an artery.

Turning more specifically to the PTO's allegation that the subgenus "stem cells" is large and thus does not advise the skilled person which stem cells to use or not use, Applicant points out that the specification describes the subject matter of claims 407-410, stem cells harvested from bone marrow and stem cells harvested from blood, at pages 40–42, and pages 47–52 wherein the specification discloses using a patient's own stem cells for growing multiple described organ species through differentiation and morphogenesis. Furthermore, the organ species artery is specifically disclosed as a desired target organ on page 52 and, as stated previously, pluripotent stem cells are described at page 50. Such disclosure, along with the functional claim requirement that an artery is grown, is believed to be sufficient to support the subgenus stem cells.

As noted above, the PTO appears to erroneously require that Applicant also disclose specific types of stem cells that do not form multiple tissue organs, i.e., that are unipotent, rather than pluripotent. Unipotent cells are well known and characterized in the medical art (and would be identified by a skilled person). Illustrative of unipotent stem cells of record in the instant

application or of record in related applications that clearly failed to form organs include: the progenitor epithelial cells of Isner; the skeletal muscle cells of the Murry et al. 1996 publication in J. Clin. Invest. entitled, "Skeletal Myoblast Transplantation for Repair of Myocardial Necrosis" cited by the Examiner in the November 28, 2003 Office Action in co-pending application Serial No. 09/836,750 (of record); and the mesenchymal cells of Caplan et al. (of record). Workers skilled in the medical arts are aware that unipotent stem cells are specific in that they are limited to promoting growth of a single tissue type, e.g., endothelium, and are incapable of promoting the growth of multiple tissue organs. It is submitted that the PTO has applied an unreasonable standard by requiring that the specification identify inoperative members of the subgenus "stem cells" in order to comply with the enablement requirement.

The PTO has also raised the issue that Applicant's disclosure does not teach the use of unfractionated (unfiltered) bone marrow mononuclear cells. Such issue is believed to be specious because there is simply no disclosure in the subject specification which would direct one skilled in the art to use a separated composition of mononuclear cells harvested from bone marrow other than an unfractionated one. The failure of the specification to teach separating and excluding any given fraction of mononuclear bone marrow stem cells is consistent with the requirement for using an unfractionated bone marrow composition and constitutes a reasonable reading of the specification. See Phillips v. AWH. Corp., 415 F. 3d 1303, (Fed. Cir. 2005). Hence, one skilled in the art would understand that the claimed stem cells harvested from bone marrow refer to an unfractionated population.

The PTO also alleged that the expressions "stem cells harvested from bone marrow" and "stem cells harvested from blood" were typically understood to refer to the CD34+ fraction. One only has to note that the post-filing date Strauer et al. publication in Circulation entitled, "Repair

of Infarcted Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in Humans" and (hereinafter "Strauer" and of record) and U.S. Patent No. 7,097,832 to Kornowksi et al. (hereinafter "Kornowski" and of record) had no such misunderstanding of the term "stem cell." Moreover, one skilled in the medical art would also be well aware of the medical art's widespread use of bone marrow transplants for treating disease. Such transplants utilize unfractionated (the entire array of bone marrow stem cells) compositions. As pointed out earlier, one skilled in the art would understand that the term "stem cells harvested from bone marrow" refers to the entire population, not to an unspecified fraction thereof. It is noteworthy that Isner, as would any other competent medical practitioner, was careful to disclose that the stem cells of his invention were separated from the entire population and then characterized.

In the previously mentioned complete internet article entitled, "Progenitor Cell Transplantation and Function following Myocardial Infarction," Dr. O'Neil acknowledges that there are two schools of thought as to which cells to use–unfiltered bone marrow (Applicant, Strauer, and Kornowski) or CD34 positive cells (Isner). In any event, one skilled in the art reading the instant specification's teaching of using stem cells harvested from the bone marrow or blood of the patient would understand that the claimed invention distinguishes from the CD34+ fraction of Isner by describing using unfiltered (global) bone marrow mononuclear cells. As pointed out earlier, there is no basis in fact for the PTO to determine that the instant specification provides guidance to one skilled in the art for implanting anything other than the entire array of bone marrow derived cells harvested from the patient's bone marrow or blood. Whether one uses the terms "global," "whole population," "unfiltered," or "unfractionated," matters not a whit. Certainly, unlike Isner, the concept of isolating/separating of a component of

the entire array of bone marrow stem cells is not implicitly or explicitly contemplated or described in the instant specification or in Strauer and Kornowski. It is clear from such disclosure what Applicant intended the term to mean, and the claims on appeal must be interpreted accordingly. See Phillips v. AWH. Corp., supra. Reading and interpreting the disclosure otherwise is improper because it distorts the reasonable meaning provided to one skilled in the art by Applicant's specification. The PTO's attempt to interpret the specification to limit stem cells to a cell population less than the whole is akin to reading new matter into the specification.

The PTO at pages 15 and 16, ¶¶17 and 18 of the 02/26/09 Office Action, asserts that the instant specification fails to provide any guidance as to how to use any kind of cell, much less a stem cell, to grow an artery. The above statement of the PTO appears to have overlooked that the claims on appeal require that the cells are stem cells. In any event, the disclosure at page 47, line 22 through page 48, line 15 of the specification clearly rebuts the PTO's notion that Applicant never clearly enunciated using stem cells (harvested from bone marrow and blood) for promoting direct differentiation and morphogenesis into an organ. Of course as admitted by the PTO, one skilled in the art would recognize that growth of an organ encompasses an artery. In any event, page 45 of the specification sets forth the well recognized medical fact that "[a]n artery is an organ from the circulatory system." PTO's statement that the specification fails to "provide any guidance as to how to use stem cells to grow an artery" evinces a lack of understanding of how differentiation and morphogenesis occurs *in vivo*. No guidance is necessary because the art skilled would recognize that once the stem cells are implanted, artery growth proceeds along genetically predetermined pathways. The fact that stem cells home to foci of ischemic tissue was known to those skilled in the art at the time of filing of the instant

specification, as evidenced by Asahara. The PTO's position that Applicant has asserted contradictory weight to Isner is not understood. In any event, the answer to the PTO's question as to how to grow an artery is remarkably simple and is reflected by the claims on appeal. One simply locally places a stem cell of the type capable of forming an artery, such as by intramuscular injection, and the body forms a bud which then grows into an artery. By disclosure, not at the direction of Isner as alleged by the PTO, "locally placing" means placing at or adjacent the site where artery growth is desired. Certainly, minimal guidance is required by one skilled in the art to perform such a notoriously old administrative procedure.

The PTO, at pages 17-22, ¶¶19-23 of the 02/26/09 Office Action, addresses Applicant's argument that the entire specification disclosure has to be considered in determining whether the enablement requirement of Section 112 has been satisfied. As recognized in the last sentence of ¶23, the PTO is charged with reading the "actual content" of the specification when rendering such determinations. Applicant maintains that a person of experience in the medical arts reading the actual content of the specification beginning at line 22, page 47 through line 15, page 48 would understand that its context contemplates reimplanting a patient's own stem cells to grow an artery as a desirable functional outcome. The PTO charges at pages 17-18, ¶20 of the 02/26/09 Office Action that Applicant has taken language from different portions of the text in order to support the claimed language. Apparently, the PTO originally failed to consider the following two paragraphs from page 48 of the specification:

> During reimplantation one of the patient's own cells is returned to the patient. During implantation, a cell not originally obtained from the patient is inserted on or in the patient.
>
> In the example above, if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro.

When read in its proper context by one skilled in the medical art, the language on page 48, line 13 of the specification "[i]n the example above…" refers to the formation (page 47, line 22) of "[o]rgans and/or tissues…formed utilizing the patient's own cells." Only an unskilled person in the medical art would be confused by the disclosures on pages 47 and 48. The PTO 02/26/09 Office Action at page 19, ¶21 apparently agrees that Applicant's interpretation is reasonable.

Applicant disagrees with the PTO's position that even if Applicant's interpretation of the specification is reasonable, it does not teach one skilled in the art how to use stem cells for growing an artery. The specification teaches that the reimplanted stem cells effect organ growth via direct differentiation and morphogenesis (page 48, lines 13-15). The specification (page 45, lines 1-4) contemplates growing an artery in the "heart, legs or other areas." The specification contemplates using bone marrow aspirant harvested from a patient (pages 40--42) as a potential source of stem cells used for the promotion of organ growth. During reimplantation, stem cell aspirant obtained from a patient's bone marrow is returned to the patient by injection at a desired location to promote the growth of an artery via direct differentiation and morphogenesis. Bone marrow transplant therapies have been in practice for decades. It is unnecessary for the specification to provide a detailed explanation of how one would go about obtaining autologous stem cell aspirant because experienced persons in the medical arts are well aware of such a procedure. Protocols for safely handling and processing such stem cell aspirant are well known and have been in practice for decades. Thus, the instant specification presents one skilled in the art with sufficient information how to obtain stem cells from a patient and how to administer these stem cells to the heart, leg, or other desired site in order to promote artery growth. Once implanted, the autologous stem cells promote growth of an artery via direct differentiation and

morphogenesis along genetically predetermined pathways. As pointed out earlier, persons skilled in the medical arts are well aware of the role of stem cells in organogenesis. Applicant submits that the specification clearly enables one skilled in the medical arts to select and obtain bone marrow aspirant from a patient and to reimplant such aspirant at a desired site in said patient to promote artery growth via direct differentiation and morphogenesis along genetically predetermined pathways.

The comments in ¶¶22 and 23 of the 02/26/09 Office Action evince a misunderstanding of Applicant's criticism of the PTO's propensity for referring to portions of the specification relating to unclaimed inventions. While it is true that it is proper for the PTO to review the whole specification in determining compliance with the first paragraph of 35 U.S.C. §112, Applicant believes that it would be more expeditious and economical on all parties to focus on portions of the specification relevant to subject matter of the claims in issue in order to develop succinct issues for appeal. Applicant believes that such practice unnecessarily results in an engorgement of the record on appeal and adds little, if any, in the way of evidence to the PTO's case in chief.

The PTO, at pages 22-27, ¶¶24-27 of the 02/26/09 Office Action, addresses the question of extrapolating dosages of VEGF cDNA to cell dosages. Applicant disagrees with the PTO's position. Initially, Applicant submits it is clear from MPEP Section 2164.01(c) that it is not necessary to specify the dosage if one skilled in the art could determine such information without undue experimentation. The PTO apparently acknowledges, at page 22, ¶24 of the 02/26/09 Office Action, that there is no enablement issue regarding the absence of guidance as to how many stem cells should be used to grow an artery. Applicant concurs with such a conclusion. The PTO states that Applicant's dosage extrapolation is only under discussion "…because

Applicant apparently seeks to establish that an extrapolation of this type is so well known in the art that it would be implicitly understood to be present in Example 18 of the specification."

Applicant never argued that an extrapolation of this type is so engrained in the prior art that it is necessarily implicit in Example 18. While Applicant agrees that dosage is not an enablement issue, nonetheless the following comments in regard to the calculus employed in the conversion is proffered in an attempt to present a complete rebuttal even at the expense of engorging the instant Response.

Applicant used a well established weight basis conversion method employed in the medical art for decades to convert the gene dosage of Example 18 to cells. Applicant never argued the viability of conversion across all species lines. Applicant's extrapolation was originally proffered in response to previous PTO criticisms regarding dosages and was presented to demonstrate if necessary how one skilled in the medical art could easily and routinely convert the gene dosage described in Example 18 to cell dosage on a mass basis. Use of such conversion based on mass is believed to be valid in this case because one skilled in the art would reasonably understand from reading the subject specification that Applicant was in possession of the concept that genes and cells are equivalent compositions for growing soft tissues in a body. The conversion was suggested solely for the purpose of illustrating that one skilled in the art desiring to employ stem cells as a VEGF growth factor equivalent in Example 18 could readily use the dosages of cDNA clones to obtain approximate equivalent cell dosage based on weight.

The PTO's statement that it is untrue that the medical art has used such conversions for the past fifty years in cell therapy because they "would not recognize the terminology or even imagine the concept of conversion depicted in Exhibit D" eschews a want of factual basis. The 02/26/09 Office Action is devoid of any objective evidence supporting such a position. It is also

apparent that Drs. Heuser and Lorincz disagree. Need the PTO be reminded that Dr. Heuser is a preeminent cardiologist associated with Bioheart in the field of cell therapy and that Dr. Lorincz has many years of experience in the medical art? In any event, both Drs. Heuser and Lorincz are quite experienced in dosage practice.

The 02/26/09 Office Action at page 24, ¶25, based on an esoteric presentation of differences between plasmid DNA and genomic DNA found in cells, attempts to explain why "it is fundamentally illogical to equate recombinant plasmid DNA to cellular DNA on the basis of mass." However, the PTO has not sufficiently explained why the reasonableness of using such weight conversion appears to be supported by the fact that such converted dosages are commensurate with those used by workers in the art using bone marrow stem cells to grow an artery, such as that reported in Strauer. The PTO alleged, at page 29 of the Final Rejection of May 5, 2008, that the above correspondence of dosages with Strauer was "pure coincidence" and that Applicant "stumbled upon" a simple method for determining cell numbers. It is clear from such unfounded characterization that the PTO has paid no deference to the conversion practice used routinely for decades by the medical art. Regarding the alleged "pure coincidence," further attention is directed to the gene and cell dosages of Isner at column 11, lines 4-9 and column 7, lines 17-23, respectively. A conversion of the dosages of nucleic acids of Isner to corresponding dosages of cells was conducted.[1]

It is evident from the conversion of nucleic acid dosages to cell dosages that the converted cell dosages fall within the range specified by Isner. The reasonableness of the

[1] Isner specified a common dosage of 2000 micrograms for the more preferably and most preferably dosage ranges. Such common dosage was utilized in the conversion calculations. The weight of nucleic acids of an average cell was considered to equal 40 picograms (pg). The 2000 microgram dosage was converted to pg by multiplying by 10^6 equals 2000×10^6 pg. An average weight of 40 pg was used for nucleic acids as consistent with the prior conversion. The conversion was then made by dividing 2000×10^6 by 40 to arrive at a cell dosage of 50×10^6 and falls with in the range specified by Isner.

conversion has been previously demonstrated regarding a conversion of the dosage of Example 18 in the instant application to the bone marrow stem cell dosages specified by Strauer. Hence, the usefulness of the well-known and established weight conversion has been attested to and demonstrated in two diverse cases. Applicant believes this fact constitutes compelling and unchallenged evidence that the PTO's criticism of the conversion is unwarranted. The Third Supplemental Declaration of Dr. Richard Heuser (of record and originally filed in co-pending application Serial No. 10/179,589) and the Second Supplemental Declaration of Dr. Andrew E. Lorincz (of record and originally filed in co-pending application Serial No. 10/179,589) confirm that the use of such well known tool is reasonable in the medical art. Accordingly, Applicant believes that the PTO's above comments are based upon unsupported speculation and opinion rather than upon objective evidence.

The PTO, at page 25, ¶26 of the 02/26/09 Office Action, incorrectly asserts that Applicant based the extrapolation calculation on the teaching of Isner. It did not happen that way; nor did Applicant assert that Isner reported a link between plasmid DNA dosage and cell dosage. All that Applicant pointed out was, like in the case of Strauer, the conversion of plasmid DNA to cells was overlapping in regard to dosages. The PTO is exercising clairvoyance in speculating that Isner did not base his cell dosages on previous work with genes. Only Isner and his coworkers know the answer to that question. The PTO has not challenged this fact except to assert that it is coincidence. Such incorrect determination formed the basis for the equally incorrect conclusion that gene therapy and cell therapy have different status in the art and, therefore, cannot be considered as functional equivalents of one another. One need look no further than Isner and Asahara to dispel such erroneous opinion. One can gather from the comments that the PTO is aware of the large doses of cells used in cell therapy, which further

mitigates any notion that dosages are critical. It is well known in the medical arts that large doses of stem cells are easily tolerated in patient's undergoing bone marrow transplants without adverse side effects.

The PTO asserts at page 26, ¶27 of the 02/26/09 Office Action that Applicant's *post hoc* derivation (extrapolation) is not implicit from any teachings in the specification. Such argument misses the point, which is that such extrapolations have been used for decades in the medical arts in regard to cell therapy and are part and parcel of the prior art. That which is well known in the art need not be included in Applicant's specification in order to comply with the enablement requirement of Section 112, first paragraph. See MPEP Section 2164.01.

Applicant submits that the dosage extrapolation and the opinions in regard thereto expressed in the Declarations of Drs. Heuser and Lorincz speak for themselves and confirm the reasonableness of Applicant's conversions. Regarding the PTO's statement that no evidence outside Applicant's declaration evidence has been provided, it is of particular note that the extrapolated dosages compare favorably (overlap) with the dosages of global bone marrow cells used by Strauer for treating myocardial infarction in human patients and in Isner for different stem cell populations and soft tissue growth, thereby confirming the reasonableness of the respective Declarants' opinions. Except to allege that such similarities are coincidence, the PTO has not demonstrated or explained why the extrapolation holds true for both Strauer and Isner. Finally, Applicant never argued that Example 18, in and of itself, explicitly suggests using stem cells to grow an artery. What Applicant asserts is that Example 18, when considered with the entire specification disclosure, would lead one skilled in the art to understand that the intramuscular injection protocol set forth therein could be used effectively with any of the

described growth factor equivalents, such as bone marrow stem cells, to grow an artery in a patient at a selected site.

The PTO, at page 26, ¶27 of the 02/26/09 Office Action, appears to mistakenly believe that the calculus is "Applicant's formula." The PTO's challenge in regard to the technical basis underlying the conversions is misdirected. Such challenge should be directed toward the originators of this well known medical tool and workers in the art who used such alleged faulty calculus—not with Applicant's experts who simply confirmed that the calculus was reasonable and found its roots in the medical art because it is notoriously well known that dosages are commonly specified on a weight basis.

The PTO's *ad hominem* criticism of Applicant's conversion fails to adequately give weight to its evidentiary value. Applicant's evidence establishes as a material fact that physicians have long used conversion charts/formulas for estimating dosages of cells from nucleic acids. It is clear from the record that cell survival and differentiation are not paramount considerations in determining cell dosages because the general practice is to employ multiple doses since stem cell overdosing has not proved to be problematic. Those skilled in the art are aware that safe dose ranges have been established over years of medical practice directed to bone marrow transplant cell therapy. The PTO's attention is again directed to the expert opinions of Drs. Heuser and Lorincz, which validate the reasonableness of Applicant's dosage conversions.

On page 27, ¶28 of the 02/26/09 Office Action, the PTO states that the specification's failure to report human clinical trials does not constitute the basis for the enablement rejection. It has been Applicant's understanding from the beginning that there is no legal standard requiring either animal or human clinical modeling. Prophetic disclosures are permitted under the rules, statute, and case law. However, the PTO concludes, without further explanation, that the lack of

actual examples "contribute significantly," i.e. was a contributing factor along with "other Wands factors," in determining of lack of enablement. It is the burden of the PTO to specifically and precisely point out why the absence of specific working examples, along with any "other Wands factors," supports a *prima facie* case of non-enablement. Applicant submits that the PTO has not met such burden.

On page 27 of the 02/26/09 Office Action, the PTO asserts one of skill in the art might surmise from Applicant's specification "...a method to use autologous stem cells to grow an artery was suggested." This assertion is consistent with pages 34 and 35, ¶36 of the 02/26/09 Office Action wherein the PTO acknowledged that, "It is plausible that cells properly described as stem cell (all claims), stem cell harvested from bone marrow (claim 407 and dependents) or stem cells harvested from blood can cause an artery to grow if they are injected locally at a selected site." Having made such statement, the PTO inconsistently attempts to limit such disclosure to merely concept rather than enabling disclosure pertaining to making and using the claimed invention and charges that not a "single enabled embodiment" of the claimed invention is shown. While asserting that actual working embodiments are not required to meet the requirements of Section 112, first paragraph, the PTO finds Applicant's specification lacking by virtue of failing to show a single organ, part of an organ, tissue, artery, or even a bud formed by placing cells in a body. Such a requirement would necessarily require Applicant to demonstrate an actual clinical model. It would appear to Applicant that the PTO is in denial of applying an improper legal standard by requiring an actual working embodiment.

On pages 28 and 29, ¶30 of the 02/26/09 Office Action, it is stated that Applicant has missed the point in regard to the citation of Isner and Kornowski as evidence of enabled disclosures dealing with "biotechnological inventions." The statement that the examples in these

patents, while not being directed to clinical trials, are not prophetic is not understood, particularly in the case of Kornowski's claims covering human treatment. The point that Applicant was attempting to make is how can the PTO deny that examples in Isner and Kornowski directed to only animal examples somehow, inexplicitly are not considered to be prophetic when applied to human patients. Perhaps, the present PTO Examiner is unaware of the well established fact that many animal experiments are not replicated when applied to humans. Hence, there can be no question that such patents were considered to be enabled by the PTO despite the lack of working examples directed to human patient, such as those generated during clinical trials.

At page 29, ¶31 of the 02/26/09 Office Action, the PTO took issue with Applicant's statement that "Applicant never intentionally, or unintentionally, linked an absence of an art rejection with proof of enablement." In response to the above points, the PTO cited a passage from Applicant's April 30, 2007, communication to the PTO. Such passage does not support the PTO's assertion. What the PTO has failed to appreciate is the manner in which the Court applied the "state of the art" factor in enablement determinations. In re Wands, 858 F.2d 731, 737, 8 USPQ 2d 1400, 1404 (Fed. Cir.1988).

The present PTO Examiner, at pages 30-33, ¶¶33 and 34 of the 02/26/09 Office Action, cited two internet articles published in The Journal of Invasive Cardiology, Vol. 17, July 1, 2005, entitled, "Progenitor Cell Transplantation and Function following Myocardial Infarction" and "Tissue Engineering and Interventional Cardiology." In the Office Action, the present PTO Examiner furnished Applicant with copies of the two above-mentioned articles (of record). Such copies contain less than the complete content of the published articles and lack proper context.

Applicant has provided complete copies of the published articles (of record) for consideration and comparison to the version furnished by the present PTO Examiner.

The two above-identified incomplete articles are relied on by the PTO to challenge Applicant's assertion of post-filing success for the claimed method. The PTO contends the furnished excerpts show that some seven years after the filing date of the instant application, skilled workers in the art voiced concerns about cell choice, dosages, time of treatment, implantation apparatus and cell survival were unanswered. Initially, Applicant's comparison of the full text of the articles with the versions furnished by the PTO clearly evinces that the present PTO Examiner has artfully selected portions of the context while omitting other portions thereof in an obvious attempt to spin the meaning of the text. Such editing raises a serious question in regard to the probative value of such material as well as the fairness of the administrative process of the PTO.

Applicant has reviewed the limited context from the excerpts presented at pages 30-33 of the 02/26/09 Office Action but disagrees that the verbage thereof rises to the level of evidence supporting non-enablement. Most of the comments concerned the BOOST, TOPCARE and Bio Heart trials. The latter body of work is dissimilar from the present invention in that it used a skeletal muscle myoblast product. Dr. Pollman from Guidant Corp. described the BOOST method, "as a simple syringe injection system loaded with 10 cc of bone marrow, 3 cc of which is applied to the coronary arteries." Dr. Pollman does not indicate that any further manipulation was necessary. Applicant has consistently taken the unanswered position that Strauer, relied upon by the PTO, describes little if any experimentation required to practice the disclosed implantation of bone marrow stem cells. Applicant makes the following comments regarding the excerpts presented by the PTO.

- The first quoted statement of Dr. O'Neil is merely asking a question that had been previously answered by Strauer.
- As Dr. O'Neil's second quoted question, neither Dr. Zelber (Guidant, Frankfort) nor Strauer reported any problem with cell hypoxia.
- Dr. O'Neil's third question virtually confirms Applicant's argument that the specification teaches using unfiltered bone marrow.
- Dr. Nikol's comments sound like professional envy rather than critical analysis of bone marrow implantation.
- Dr. Gonschior's comments merely affirm that intravenous infusion would be the simplest method while Strauer's endocardial delivery may be the most efficient. These comments mirror the views expressed by Strauer.
- The quoted comments by Dr. Holmes merely express his criticism of premature human trials and appears to be especially directed to systemic infusion of cells.

Dr. Whitlow's quoted comments are purely theoretical and do not evince that his opinions are based on the performance of any experimental or clinical trials. The autopsy findings described in the Dohmann et al. 2005 publication in Circulation entitled, "Transendocardial Autologous Bone Marrow Mononuclear Cell Injection in Ischemic Heart Failure" cited in the Examiner's Answer dated November 28, 2007 in co-pending application Serial No. 09/794,456 (hereinafter "Dohmann" and of record) show that Dr. Whitlow's theoretical premises are not well founded.

It is puzzling that the PTO can conclude from such selective utterances that "[t]here was a general agreement that more experimentation was needed." This is particularly telling when one understands that the later work of Dohmann and Kornowski closely parallel the work of Strauer and produced similar results.

One final point remains. What is most disturbing to Applicant regarding the PTO's use of these two articles is the omission of information favoring enablement of Applicant's claimed method. For example, the PTO omitted the statement by Dr. Nikol that, "cells are considered a blood product" and the statement by Dr. O'Neil that, "…because these bone marrow cells are pluripotential..." A further example is the spontaneous utterance of Dr. Heuser that, "[t]he first time I saw this technique presented by the group [TOPCARE] in Frankfort, I was astonished at how simple it actually was," and Dr. Pollman's statement that, "a simple syringe injection system" was used for implantation. Also absent is any reference to Dr. O'Neil's statement regarding "the cascade of processes that actually allow a new cell to come in and regenerate." It is tempting to speculate that the present PTO Examiner's omission of such comments by Drs. Pollman, Heuser, and O'Neil could be attributed to the Examiner's carefully refraining from identifying relevant evidence supporting arguments made by Applicant in this and in the companion applications of Dr. Elia. In any event, once one skilled in the art realizes that bone marrow promotes the growth of arteries the delivery of the bone marrow is simple. Furthermore, the above utterances indicate that the treatment is not complex as alleged by the PTO. The answer to the PTO's irrelevant question, "Why didn't "[Dr. Heuser] enlighten his colleagues?" is straightforward. Being a patentee in his own right, Dr. Heuser fully comprehends his duty in regard to confidential information, even if the present PTO Examiner is dismissive of such duty. Dr. Pollman, an employee of Guidant, was aware of confidentiality obligations regarding privilege information, as were all of the others. See Dr. Pullman's comment near the bottom of the first page of the "Progenitor Cell Transplantation and Function Following Myocardial Infarction" article (of record). In addition, an opinion regarding enablement based upon the

disclosure of a patent application is distinct from optimizing medical processes and continuing research involving such processes. The present PTO Examiner's query misses this point.

The PTO, at pages 34 and 35, ¶36 of the 02/26/09 Office Action, states that:

> It is plausible that cells properly described as "stem cell" (all claims), "stem cell harvested from bone marrow" (claim 407 and dependents) or "stem cells harvested from blood" can cause an artery to grow if they are injected locally at a selected site.

The present PTO Examiner further characterized the invention to be a series of respectable guesses that later proved true. However, the present PTO Examiner then denied the fact that post-filing references demonstrated that the disclosed and claimed invention confirmed the claimed results. Instead, such post-filing work was credited as being evidence of further experimentation involved in the act of invention. Such characterization is factually inaccurate. Although the PTO did not identify specific post-filing references in the 02/26/09 Office Action, the post-filing Strauer publication performs the same steps as claimed and achieves the same results. The record will show that when repeatedly challenged by Applicant to point out where Strauer performed any experimentation, the PTO was not able to identify any such alleged experimentation.

Strauer does not describe using any experimental protocol to determine appropriate cell population, i.e., there is no requirement for using a specific subset of bone marrow stem cells. Regarding time of treatment, Strauer does not disclose that determining time of treatment required experimentation. It is clear from the record that the treatment of myocardial infarction (MI) in human patients exhibiting either acute or chronic disease is considered. Strauer elected to treat patients from five to nine days after suffering an MI. Note that Strauer 2005 discloses treating chronic MI in patients that had transmural MI some 27 months earlier. Again, no

experimentation regarding treatment time was noted. It is evident that the time of treatment following an MI is not a critical variable and undue experimentation would not be required. To the extent that the PTO may be relying on Strauer to establish that the time of administration is critical, Applicant points out that Strauer 2005 is the "best evidence" in regard to whether time of treatment in human patients is critical. Strauer 2005 teaches that stem cells can be used to successfully treat MI in human patients suffering either acute or chronic disease. Moreover, Isner also does not indicate that time is critical in the treatment of humans exhibiting ischemic heart tissue and this was not viewed as an impediment by the PTO. Thus, the PTO's conclusion that unidentified "further experimentation" would be required to practice the claimed invention is not supported on the record and is fatally flawed.

Applicant believes that the above-mentioned lack of experimentation by Strauer actually demonstrates the converse of the present PTO Examiner's hypothesis, i.e., that one skilled in the art would be able to make and use Applicant's so-called "plausible" invention without recourse to experimentation of any kind, let alone an undue amount of experimentation.

As a final point, the PTO, at page 35, ¶37 of the 02/26/09 Office Action, refers to the breadth of claims, the amount of direction or guidance, and the presence or absence of working examples as evidence of that undue experimentation would be required to practice the claimed invention. Although the PTO did not specifically rely upon In re Wands, supra, in this portion of the 02/26/09 Office Action, it is assumed that the PTO may have intended to rely upon such decision due to the presented analysis. In In re Wands, the Court focused on three factors: the state of the prior art, the level of skill in the art, and the amount of direction provided by the specification. The specification (pages 47-48) clearly describes the concept of implanting a patient's own cells (autologous stem cells) to promote differentiation and morphogenesis into an

organ, which by disclosure includes an artery. The specification teaches numerous methods of implantation including intramuscular injection. The PTO's allegation that the specification fails to address complex problems "that might be encountered" in stem cell therapy is a "red herring," which has not been factually supported on the record. Contemporary prior art wisdom (Isner and Asahara) at the time of Applicant's invention demonstrates the conventionality of intramuscular injection of stem cells and genes in treating disease involving ischemic tissue. Contrary to the PTO's assertion, the post filing work of Strauer does not describe solving any complex problems associated with implanting bone marrow stem cells. Neither the contemporary nor post- filing art disclose any specific problems that had to be addressed and overcome in order to successfully implant cells in a human patient. Thus, the PTO's determination that the specification is non-enabling because it fails to address nonexistent problems is inauthentic.

Applicant believes the instant fact situation is similar to that of In Re Wands because the skill level is high and known administration techniques and known materials are utilized in the practice of the invention. In addition to such factual parallelism, Applicant provided expert objective evidence in Paragraph 7 of the Fourth Supplemental Declarations of Drs. Heuser and Lorincz (of record). These medical experts read portions of the specification setting forth the generic growth factor invention and claimed and non-claimed species of such generic invention and determined that one skilled in the medical arts, armed with the guidance and direction in the relevant specification disclosures, would be enabled to practice the methods defined in the claims on appeal and to predictably anticipate the results defined therein without need for resorting to undue experimentation. When the guidance and direction provided by Applicant's specification disclosure, the level of knowledge and the content of the prior at the time of the invention, such as that of Isner, Asahara and Nabel, as established in the record and Applicant's declaration

evidence are interpreted in a reasonable manner, an analysis considering the Wands factors compels a conclusion that undue experimentation would not be required to practice the invention called for in the appealed claims.

In summary, Applicant believes that the PTO failed to provide sufficient objective evidence or reasoning to support a determination of lack of enablement under current law when considered *vis-à-vis* the evidence of enablement provided by Applicant's specification. Thus, the PTO has failed to establish a *prima facie* case of lack of enablement, and this rejection should be withdrawn.

Assuming, *arguendo*, that the PTO somehow met the burden of establishing a *prima facie* case of lack of enablement, Applicant believes that any such case has been rebutted by the submission of Declarations of experts in the field – Drs. Meger, Lorincz, and Heuser. The conclusions set forth in the respective Declarations establish and rely upon objective facts that are material to a determination of enablement. Dr. Meger's Declaration established that the disclosed administration techniques were known as of the filing date of the application. Regarding the Declarations of Drs. Lorincz and Heuser, these highly skilled medical experts read, understood, and relied upon relevant portions of the specification, including portions relating to the growth factor genus and species thereof, and based upon such objective facts, reached the determination that one skilled in the medical art, armed with the knowledge in the disclosures, would be enabled to practice the claimed method and to predictably anticipate the results defined therein without need for resorting to undue experimentation.

Applicant further points out that Drs. Heuser and Lorincz, in Paragraph 7 of their above-mentioned respective Fourth Supplemental Declarations, noted specific disclosures in the specification and stated that such disclosures related to using a growth factor for promoting the

growth of soft tissue, and more specifically, to a method of using a cell, such as a stem cell, to grow soft tissue, such as an artery. Such statements rely in-part upon Applicant's disclosure at pages 40-42, which describe stem cells harvested from bone marrow, harvested from blood or from cell culture techniques, which differentiate during morphogenesis to form organs. Applicant believes that the expert opinions of Drs. Heuser and Lorincz, based upon their complete reading of the specification, fully rebut the PTO's position and confirm that of Applicant. Hence, the PTO's contention that the specification does not describe and enable a skilled medical person to grow an artery with use of a cell is erroneous.

The PTO, at page 30, ¶32 of the 02/26/09 Office Action, states that consideration has been given to the Declarations of Dr. Heuser and Dr. Lorincz (ten declarations of record) but concludes that opinions of experts in regard to the ultimate legal conclusion of enablement are entitled to no weight, citing In re Lindell and In re Chilowsky for precedent. The cited case law was purported to stand for the proposition that enablement is a question of law. However, it is clear from MPEP 2164.05 that declarations are evidence that must be considered and that weight must be accorded based on the factual evidence presented therein supporting a conclusion of enablement. The Court in In re Buchner, supra, held that "expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement." In Buchner, the PTO determined that the specification lacked enablement because elements necessary for carrying out the invention were neither disclosed therein nor well-known to those of ordinary skill in the art. The Court, while recognizing that the Buchner specification need not disclose what is well known in the art, agreed with the PTO that unless the identified missing elements were well-known in the art that the application must provide such information and that "it is not sufficient to provide it only through an expert's declaration." The present factual pattern is

clearly distinct from that of Buchner in that the PTO has conceded that the administration of cells was known in the medical art at the time of the present invention (See page 22, first paragraph, of the September 22, 2006 Final Rejection issued in co-pending application Serial No. 09/836,750 and of record). It is further established in this record that the compositions (stem cells, such as bone marrow stem cells), implantation apparatus (hypodermic needle) and treatment methods disclosed in the specification were well-known in the medical art. Contrary to the PTO's position, Applicant's evidence of enablement is supported by more than Declarants' conclusory statements. Declarants identify and rely upon facts, i.e., specific portions of the disclosure in the instant specification which supports their conclusions that one skilled in the art would be able to make and use the claimed invention. Declarants' reading and understanding of the previously identified portions of the specification mentioned in Paragraph 7 of the above-mentioned Fourth Supplemental Declarations of Dr. Heuser and Dr. Lorincz, compels a conclusion that Dr. Elia was in possession the concept of implanting bone marrow stem cells and growing arteries in a human patient.

A concise reading of the multiple Declarations of Drs. Heuser and Lorincz reveals that these experts relied upon the guidance and direction in the application's generic and specific disclosures pertaining to the claims coupled with their skills and experiences in the medical art in rendering their conclusions. Applicant, likewise, relies upon such disclosure.

Other than stating at page 30, ¶32 of the 02/26/09 Office Action that the PTO's position can be found in the record, the probative value of Applicant's evidence has not been assessed. Rather, the declaration evidence has been dismissed as "not persuasive." By failing to articulate adequate reasons to rebut the Declarations of Drs. Heuser and Lorincz, the PTO "failed to consider the totality of the record for the purpose of issuing a final rejection and thus erred as a

matter of law." In re Alon, 76 F.3d 1168, 37 USPQ2d 1578 (Fed.Cir. 1996). It is trite law that the PTO must consider the probative value of such evidence *vis-à-vis* any asserted *prima facie* case. See In re Oetiker, at 1445, 24 USPQ 2d at 1444. In re Keller, 642 F.2d 413, 208 USPQ 871, (CCPA 1981). In the absence of critical analysis, the PTO appears to be relying solely upon its opinion rather than assessing weight to the objective evidence proffered in the Declarations. PTO Examiners, not being skilled persons in the medical art, must give weight to these expert opinions rather than substitute personal opinions. See In re Neave, 370 F.2d 961, 152 USPQ 274, (CCPA 1967).

The PTO's attention is respectfully directed to In re Wands, 858 F.2d 731, 737, 8 USPQ 2d 1400, 1404 (Fed. Cir.1988), which decision led to the grant of a patent. The Court found that the PTO's determination of nonenablement was unsupported by the evidence in the record. The Court further noted that the skill level in the art was high and that known materials were utilized in the practice of the invention in weighing the evidence. The instant fact situation is similar to that of In re Wands, supra because the skill level is also high and known administration techniques and known materials are also utilized in the practice of the invention. In addition to such factual parallelism, Applicant provided expert objective evidence in the form of the Declarations of Drs. Heuser and Lorincz. These medical experts read relevant portions of the specification setting forth the generic invention and elected and non-elected species of such generic invention and determined that one skilled in the medical art, armed with the guidance and direction in the specification disclosures, would be enabled to practice the methods defined in the claims on appeal and to predictably anticipate the results defined therein without need for resorting to undue experimentation. Regarding complexity, the PTO is again referred to the spontaneous utterances mentioned above wherein the process was characterized as being simple